1) the total number of the non substituted NH_3^+ functions is of at least 50 % of the polymerization degree,

2) the number of monomers initially carrying free NH_3^+ is substituted in a ratio of at least 50 % of the polymerization degree by residues leading to a destabilization of the cellular membrane.

R E M A R K S

Responsive to the determination of lack of unity set forth in the Official Action of September 24, 2002, Applicants hereby provisionally elect Group IV, claims 9, 10, 17 and 19, drawn to a composition comprising an oligomeric conjugate and an oligonucleotide, with traverse.

The grounds for traverse are as follows:

The same claims as pending in the present national stage application were subject to examination during the international phase of the PCT application. While the WO 98/22160 publication is cited by the Official Action as allegedly showing that the technical feature linking the inventions does not constitute a contribution over the prior art, Applicants note that the WO 98/22160 publication was also considered by the International Examiner. However, the International Examiner found no lack of unity, applying the same legal standards to the identical facts. Thus, the U.S. Patent Office cannot now contend that examination of the pending claims in the present application would pose an undue searching burden. Indeed, the U.S. examiner

has the considerable benefit of search results generated by the International Examiner.

Furthermore, the Official Action does not explain why applying the identical legal standards to the identical claims, the opposite result is now being reached in the present U.S. national phase application, relative to the international application.

Moreover, Applicants respectfully traverse the assertion that the WO 98/22610 publication satisfies the requirements of PCT Rule 13.2. It is believed that the WO 98/22610 publication fails to show the special technical feature of the present invention.

In document WO 98/22610, it is disclosed that the NH_3^+ functions of monomers, constituting the unit of the polymer, may be substituted by protonable residues in a weak acid medium, only with a ratio ranging from 10 to 45% (See WO 98/22610, page 6, lines 14-16, page 9 lines 6-7, page 14, lines 16-17, page 15, line 18, imidazole nucleus is protonated in weak acid medium, p17 line 4).

The Examiner's attention is respectfully directed to the polymeric groupings defined in WO 98/22610 at pages 15 and 16 of the publication. Formula I is disclosed on page 15 and formula II is disclosed on page 16. The polymeric groups of formula I are described as groups which contain "radicals R among which: 10% to 45% [are] residues carrying an imidazole nucleus and optionally a free NH_3^+ [...], 10% to 90% of the number of

radicals R representing free *W*-amino NH_3^+...". The same terms are used to describe formula II, except that the term "10% to 90%" is substituted with "30% to 90%". It is believed that this difference does not fundamentally change the complex. Thus, the 10% to 90% term corresponds to the ratio of R radicals having a free *W*-amino NH_3^+ and not to the ratio of R radicals representing protonable residues in weak acid medium.

In fact, this latter ratio is represented by the range "10% to 45%". The complexes described by formula I and formula II may be understood as the combination of the ratio of R representing 10% to 45% protonable residues in a weak acid medium and the ratio of R representing for 10% to 90% of free *W*-amino NH_3^+. Hence, it is noted that the ratio of radicals R representing protonable residues in weak acid medium does not exceed 45%.

In the present invention, it is noted that "the free NH_3^+ of [monomeric components] are substituted in a ratio of at least 50%, advantageously from 60% to 95%, particularly 80% to 90%, by protonable residues in a weak acid medium" (See the present specification, page 3, lines 8 to 12, and claim 1). Moreover, all of the oligomeric conjugates synthesized in order to illustrate the present invention have a ratio of substitution of NH_3^+ functions of monomers by protonable residues in a weak acid medium greater than 50% (See present specification at pg 33-35, examples 1-3).

Thus, it is believed that the present invention is distinct and non-obvious from the WO 98/22610 publication, and

that the WO 98/22610 publication fails to satisfy the art-based requirement of PCT Rule 13.2.

Applicants note that the polymer described in WO 98/22610 may comprise a degree of polymerization ranging from "15 to 900, preferably 100 to 300" (See WO 98/22610, page 15, line 15) or "preferably 200" (See. WO 98/22610, 21, line 24). However, it is also noted that the choice of a ratio of substitution by residues recognized as signal molecules by membrane receptors are given for polymers comprising 200 units of monomers (See WO 98/22610, page 11, line 29 to page 12, line 10, page 14, lines 25-28, page 16, lines 3-5, page 22, lines 5 to 15). In addition, it is noted that the examples that illustrate the synthesis of the polymer comprise a degree of polymerization of 190 (See WO 98/22610, page 40 and following, legends of figures 1 to 9).

Hence, the WO 98/22610 publication teaches that it is preferable to use a degree of polymerization of 100 to 300 (See WO 98/22610, page 15, line), and preferably 200 (See WO 98/22610, page 15, line 15, and page 21, line 4). This is confirmed by the results presented in Table I on page 39 of the present specification (See lines corresponding to DP of 36 and 19 in combination with a His % ranging from to 22 to 45, Table I, page 39). Thus, it can be concluded that the WO 98/22610 publication corresponds to a polymer having a degree of polymerization of about 200.

The present invention utilizes a degree of polymerization ranging from 5 to 50 (See the present

specification, page 3, line 4, page 9, line 23, and claim 1). In fact, the examples in the present specification demonstrate a degree of polymerization ranging from 17 to 20 (See the present specification, pages 33 to 34, examples 1 and 2; pages 37, examples 5 and 6).

Although the degree of polymerization described in the present invention overlaps the degree of polymerization for that of WO 98/22610, it is observed that it is far from that which is used in the WO 98/22610 publication. Furthermore, the range of degree of polymerization described in the present specification is narrower than that which is described in the WO 98/22610 publication. The use of this range of polymerization to obtain oligomeric conjugates leads to a technical effect distinct from that obtained in the WO 98/22610 publication. That is to say, the oligomeric conjugate obtained allows for the transfer of oligomers which could not be obtained with the teachings of the WO 98/22610 publication (See present specification, Table I, page 39).

Thus, it can be appreciated that the choice of the range of polymerization described in the present invention leads to a distinct and non-obvious product that is not described in the WO 98/22610 publication. It is believed that the difference between the present invention and WO 98/22610 corresponds to the selection of a specified range of polymerization combined with a ratio of substitution of NH_3^+ groups of monomer units by

protonable residues in a weak acid medium, which is at least equal to 50%, and preferably ranges from 80% to 90%.

In light of the WO 98/22610, it is believed that the publication fails to disclose or suggest the claimed invention to one of ordinary skill in the art. The WO 98/22610 document teaches a means to transfer into cells a long sequence of nucleic acid (gene or plasmid, See WO 98/22610, page 1, line 1 to 11, page 20, lines 26 to 32, page 21, lines 1 to 21, and page 39 line 28). However, as the results show in Table I on pages 38 and 39 of the present specification, the use of this polymer is inappropriate to transfer oligomers into cells. Nothing in the disclosure of the WO 98/22610 publication would lead one of ordinary skill in the art to the specified range of polymerization and increased ratio of monomer units substituted by protonables residues in a weak acid medium to obtain oligomeric conjugates that allow cell transfection of oligomers.

In conclusion, it is believed that it has been demonstrated that the WO 98/22610 fails to disclose or suggest the special technical feature of the present invention. Thus, it is respectfully submitted that the WO 98/22610 publication cannot be cited as showing the special technical feature linking the inventions under PCT Rule 13.2.

At the very least, Applicants submit that claims 11 and 14 should be examined with Group IV. Claim 14 is related to a method for the in vitro, ex vivo or in vivo transfer of an oligonucleotide that is used under the form of a composition as

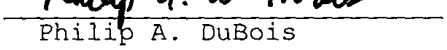
set forth in claim 9. Hence, the unity of invention between claims 9 and 14 is kept with respect to the composition comprising an oligomeric conjugate and an oligonucleotide. Claim 11 is related to the use of an oligomeric conjugate for the in vitro, ex vivo, in vivo transfer of biological molecules. Thus, it is respectfully submitted that the unity of invention between claims 9, 11 and 14 is apparent.

In light of the above discussion, therefore, it is believed that the Applicants are entitled to an action on the merits of all the pending claims in the present application, in their full scope. At the very least, it is respectfully submitted that Group IV and VII should be examined together. Such action is accordingly respectfully submitted.

Attached hereto is a marked-up version of the changes made to the specification. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

YOUNG & THOMPSON

By 

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claim 1 has been amended as follows:

--1. (amended) Oligomeric conjugate positively charged, containing an oligomer with a polymerization degree (PD) from 5 to 30 [50, preferably 10 to 40 and more preferably 20], formed from monomeric components having free NH_3^+ in a number equal to or higher than 50 % of the polymerization degree,

said oligomer being as follows:

- the free NH_3^+ of the above-mentioned components are substituted in a ratio of at least 50 %, advantageously from 60 % to 95 %, particularly 80 to 90 % (this ratio being determined by nuclear magnetic resonance), by protonable residues in a weak acid medium, leading in such a weak acid medium to a destabilization of cellular membranes,

- the above-mentioned protonable residues posses in addition the following properties:

→ they contain a functional group enabling them to be linked to the above-mentioned oligomer,

→ they do not correspond to a recognition signal recognized by a cellular membrane receptor,

→ they can comprise at least one free NH_3^+ group,

- the free NH_3^+ of the above-mentioned monomers can be also substituted by an uncharged residues leading to a reduction of the number of positive charges in comparison to the same oligomeric before substitution,

- molecules constituting a recognition signal recognized by a membrane cellular receptor may be present:

→ either by substitution of some of the free NH_3^+ of the above-mentioned monomers,

→ either on some of the uncharged residues leading to a reduction of the number of charges,

→ either on some of the above-mentioned protonable residues leading to a destabilization of the cellular membranes,

→ or by substitution of the free NH_3^+ (if it is present) of the above-mentioned protonable residues leading to a destabilization of the cellular membrane,

provided that:

1) the total number of the non substituted NH_3^+ functions is of at least 50 % of the polymerization degree,

2) the number of monomers initially carrying free NH_3^+ is substituted in a ratio of at least 50 % of the polymerization degree by residues leading to a destabilization of the cellular membrane.--